

## REMARKS

Claims 1 and 3-21 are all the claims pending in the present application, claim 2 having been canceled without prejudice or disclaimer as set forth above. Claims 1, 3, 5, 7-11, 17, and 18 have been amended to correct typographical errors, to provide proper antecedent basis, and to recite aspects of the disclosed subject matter with more particularity. Support for the foregoing amendments is found throughout the present application; no new subject matter has been added.

Initially, Applicants thank the Examiner for indicating that claims 3-6, 8, 12-16, 20, and 21 are directed to allowable subject matter.

Claims 11 and 17 are objected to based upon an informality arising from a typographical error, and additionally stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. Applicants respectfully submit that the foregoing amendments adequately address the informality noted by the Examiner. Additionally, Applicants direct the Examiner's attention to the specification for support of the foregoing amendments, and particularly to Equations 13-15 set forth on page 6 (supporting the "mean . . . of the covariance" recited in claim 11) and to the discussion spanning pages 4-6 (supporting the "slope of a linear regression" recited in claim 17). Applicants submit that claims 11 and 17 are definite, and request that the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim 1 stands rejected under 35 U.S.C. §102(b) as anticipated by the paper (Biologist's perspective on analytical imaging systems as applied to protein gel electrophoresis) to Patton (Patton). Claims 7 and 17-19 stand rejected under 35 U.S.C. §102(e) as anticipated by United States Patent (USP) 6,411,741 to Hamamura et al. (Hamamura). Claim 11 stands rejected under 35 U.S.C. §102(b) as anticipated by USP 5,208,870 to Ennis. Claim 2 stands rejected under 35 U.S.C. §103(a) as unpatentable over Patton in view of USP 6,319,682 to Hochman. Claims 9 and 10 stand rejected under 35 U.S.C. §103(a) as unpatentable over Hamamura in view of USP 6,251,601 to Bao et al. (Bao). Applicants respectfully traverse the prior art rejections, and request reconsideration and allowance of all the pending claims based upon the following remarks.

Aspects of the present invention relate generally to DNA microarray analysis, and more particularly to statistical analyses using error estimates from image based metrics to analyze data acquired from microarrays. As set forth in detail throughout the present application, statistical

methodologies as described and claimed involve extracting quantitatively accurate ratios from pairs of images.

As set forth in more detail below, Applicants submit that the references cited are more deficient than the Examiner acknowledges, and that the prior art rejections are therefore improper. In that regard, it is noted that a reference can anticipate a pending claim under the various subsections of 35 U.S.C. §102 if, and only if, that reference explicitly teaches (or inherently embodies) every limitation recited in the pending claim. Similarly, where references are combined under 35 U.S.C. §103, the combination must teach every recited limitation in order for the Examiner to establish a *prima facie* case of obviousness.

#### The Rejection Under 35 U.S.C. §102(b) -- Patton

Claim 1 stands rejected under 35 U.S.C. §102(b) as anticipated by Patton. In accordance with the fair teachings of the Patton paper, however, the disclosed methodologies use *regional background measurements from histograms* to fit the profile of the background intensity pattern (see, e.g., the discussion at page 71 of Patton). As an example of such a background intensity pattern, the region between spots in Figure 5 of Patton is illustrative.

In contrast, the methods set forth in the present application, and as particularly recited in pending claim 1, employ a best-fit method to determine the background *from the entire data set* based upon spot intensity ratios (as opposed to Patton's histogram analysis of image sub-regions). In particular, the method of pending claim 1 recites both "selecting a plurality of spots within the image falling within a least squares curve fit; and *responsive to the selecting*, determining a constant background intensity . . . ." The Patton paper fails to teach or even to suggest determining a constant background intensity responsive to such a least squares fit. The rejection under 35 U.S.C. §102(b) is therefore improper.

Applicants respectfully submit that Patton is deficient at least to the extent that the paper fails to teach or even to suggest every element recited in claim 1; independent claim 1 is allowable at least for the reasons set forth above.

#### The Rejection Under 35 U.S.C. §102(e) -- Hamamura

Claims 7 and 17-19 stand rejected under 35 U.S.C. §102(e) as anticipated by Hamamura. Applicants note initially that, as understood by an ordinarily skilled artisan, the term "coefficient

Of variation” represents generic phraseology used in the field of statistical analysis; in that regard, the term generally refers to a ratio of any standard deviation with respect to its corresponding mean (*i.e.*, “coefficient of variation” = standard deviation/mean). Accordingly, to the extent that the Examiner has relied upon Hamamura as teaching determination of “a coefficient of variation,” Applicants submit that such a teaching would be unremarkable.

Equation 18 on page 7 of the present application provides for computation of one embodiment of a “coefficient of variation” *of a ratio*. In that regard, pending claim 7 explicitly recites an element directed to “determining a ratio coefficient of variation.” Hamamura’s coefficient of variation, on the other hand, involves only background intensity values, and is calculated in accordance with a very different principle (and a very different methodology) than that contemplated in Equations 16 and 18 of the present application, for example. Further, Hamamura neither teaches nor suggests a ratio coefficient of variation, in any event.

Additionally, at column 8, lines 27-40, for example, the Hamamura patent refers to plots of density (*i.e.*, intensity) versus density gradient (intensity derivative), rather than to plots of coefficient of variance and variance as described and claimed in the present application. The histograms used by Hamamura bear no relation to a plot of covariance versus variance; in particular, pending claim 17 specifically recites “determining a slope of a linear regression between the covariance and the variance.” The Hamamura patent fails to teach, among other elements in claim 17, at least this particular feature.

Applicants respectfully submit that the Hamamura patent is deficient at least to the extent that it fails to teach or even to suggest every element recited in claims 7 and 17 as set forth above; claims 7 and 17-19 are allowable at least for the foregoing reasons.

#### The Rejection Under 35 U.S.C. §102(b) -- Ennis

Claim 11 stands rejected under 35 U.S.C. §102(b) as anticipated by Ennis. Initially, Applicants note that “covariance” is another example of a generic statistical term. The covariance calculated by Ennis is designed to measure a substantially different image property than the two channel microarray covariance calculation as disclosed and claimed in the present application. In that regard, Ennis contemplates calculating a “covariance” from data obtained from sub-regions within a single channel image. The covariance employed to analyze microarrays as described and claimed in the present application, on the other hand, is calculated

from different equations using different principles (e.g., involving two-image data) as set forth in detail, for example, in the discussion bridging pages 7-10 of the present application.

⇒ Specifically, the Ennis patent neither teaches nor suggests determining and normalizing a covariance as described in the present application and as recited with particularity in claim 11. Accordingly, the fair teachings of Ennis are insufficient to anticipate the recited method, and Applicants respectfully submit that claim 11 is allowable at least for the foregoing reasons

#### The Rejections Under 35 U.S.C. §103(a)

Claim 2 stands rejected under 35 U.S.C. §103(a) as unpatentable over Patton in view of Hochman. As indicated briefly above, claim 2 has been canceled without prejudice or disclaimer; Applicants reserve the right to pursue the subject matter recited in claim 2 in a continuation application.

Claims 9 and 10 stand rejected under 35 U.S.C. §103(a) as unpatentable over Hamamura in view of Bao. The Examiner has failed to appreciate, however, that the Bao patent fails to supply the deficiencies of the Hamamura patent set forth above with particular reference to claims 7 and 17. Specifically, neither Bao nor Hamamura suggests a ratio coefficient of variation; while Hamamura considers a coefficient of variation involving background intensity values, this patent, even in combination with the Bao patent, fails to teach the ratio coefficient of variation described in the present application and recited in claim 7. Accordingly, the combination of the Bao and Hamamura patents is insufficient to render obvious pending claims 9 and 10.

Since the references, when considered either independently or in combination, fail to teach or to suggest every element recited in the pending claims, the Examiner has failed to establish a *prima facie* case of obviousness with respect to claims 9 and 10. Applicants respectfully submit that claims 9 and 10 are allowable at least for the reasons set forth above with reference to claim 7. Additionally, claims 9 and 10 include additional subject matter, and are additionally allowable for their respective recitations.

### CONCLUSION

Based at least upon the foregoing Remarks, Applicants respectfully submit that all the pending claims are allowable, and that the present application is currently in condition for allowance. The Examiner is encouraged to contact the undersigned at 858-509-4007 if it is believed that a discussion may advance the prosecution of this case.

Applicants believe that a fee is required at this time. Please apply any charges or credit any overpayments to Deposit Account No. 50-2212.

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Respectfully submitted,  
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